

TENT COOPERATION TRE

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 August 1999 (18.08.99)	
International application No. PCT/US98/25314	Applicant's or agent's file reference P98022WO
International filing date (day/month/year) 27 November 1998 (27.11.98)	Priority date (day/month/year) 28 November 1997 (28.11.97)
Applicant BRADFIELD, Christopher, A. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

25 June 1999 (25.06.99)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Jean-Marie McAdams Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

REED, Janet, E.
Dann, Dorfman, Herrell and Skillman
Suite 720
1601 Market Street
Philadelphia, PA 19103
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year)

10 June 1999 (10.06.99)

Applicant's or agent's file reference

P98022WO

IMPORTANT NOTICE

International application No.

PCT/US98/25314

International filing date (day/month/year)

27 November 1998 (27.11.98)

Priority date (day/month/year)

28 November 1997 (28.11.97)

Applicant

WISCONSIN ALUMNI RESEARCH FOUNDATION et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU,CN,EP,IL,JP,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,
ID,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,
SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on

10 June 1999 (10.06.99) under No. WO 99/28464

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J. Zahra

Telephone No. (41-22) 338.83.38

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT) -

<p>(51) International Patent Classification ⁶ : C12N 15/12, C07K 14/47, C12N 15/11, C07K 16/18, G01N 33/50</p>	<p>A2</p>	<p>(11) International Publication Number: WO 99/28464 (43) International Publication Date: 10 June 1999 (10.06.99)</p>
<p>(21) International Application Number: PCT/US98/25314 (22) International Filing Date: 27 November 1998 (27.11.98) (30) Priority Data: 60/066,863 28 November 1997 (28.11.97) US (71) Applicant (for all designated States except US): WISCONSIN ALUMNI RESEARCH FOUNDATION [US/US]; 614 Wal- nut Street, Madison, WI 53705 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRADFIELD, Christo- pher, A. [US/US]; 4206 Mohawk Avenue, Madison, WI 53706 (US). GU, Yi, Zhong [CN/US]; University of Wis- consin, McArdle Laboratory for Cancer Research, Room 213, 1400 University Avenue, Madison, WI 53706 (US). HOGENESCH, John, B. [US/US]; University of Wisconsin, McArdle Laboratory for Cancer Research, Room 213, 1400 University Avenue, Madison, WI 53706 (US). (74) Agents: REED, Janet, E. et al.; Dann, Dorfman, Herrell and Skillman, Suite 720, 1601 Market Street, Philadelphia, PA 19103 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>
<p>(54) Title: CDNAS AND PROTEINS BELONGING TO THE bHLH-PAS SUPERFAMILY OF TRANSCRIPTION REGULATORS, AND METHODS OF USE</p> <p>(57) Abstract</p> <p>The present invention provides isolated nucleic acids and proteins that are new and distinct members of the bHLH-PAS superfamily of transcription regulators. These "MOPs" (members of PAS) are useful in a variety of research, diagnostic and therapeutic applications. Several of the MOPs of the present invention are α-class hypoxia-inducible factors. Several other of the MOPs of the invention are involved in circadian signal transduction.</p>		

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/12, C07K 14/47, C12N 15/11, C07K 16/18, G01N 33/50	A3	(11) International Publication Number: WO 99/28464 (43) International Publication Date: 10 June 1999 (10.06.99)
(21) International Application Number: PCT/US98/25314 (22) International Filing Date: 27 November 1998 (27.11.98) (30) Priority Data: 60/066,863 28 November 1997 (28.11.97) US (71) Applicant (for all designated States except US): WISCONSIN ALUMNI RESEARCH FOUNDATION [US/US]; 614 Wal- nut Street, Madison, WI 53705 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRADFIELD, Christo- pher, A. [US/US]; 4206 Mohawk Avenue, Madison, WI 53706 (US). GU, Yi, Zhong [CN/US]; University of Wis- consin, McArdle Laboratory for Cancer Research, Room 213, 1400 University Avenue, Madison, WI 53706 (US). HOGENESCH, John, B. [US/US]; University of Wisconsin, McArdle Laboratory for Cancer Research, Room 213, 1400 University Avenue, Madison, WI 53706 (US). (74) Agents: REED, Janet, E. et al.; Dann, Dorfman, Herrell and Skillman, Suite 720, 1601 Market Street, Philadelphia, PA 19103 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims</i> <i>and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 11 November 1999 (11.11.99)
(54) Title: CDNAS AND PROTEINS BELONGING TO THE BHLH-PAS SUPERFAMILY OF TRANSCRIPTION REGULATORS, AND METHODS OF USE		
(57) Abstract <p>The present invention provides isolated nucleic acids and proteins that are new and distinct members of the bHLH-PAS superfamily of transcription regulators. These "MOPs" (members of PAS) are useful in a variety of research, diagnostic and therapeutic applications. Several of the MOPs of the present invention are α-class hypoxia-inducible factors. Several other of the MOPs of the invention are involved in circadian signal transduction.</p>		

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P98022WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 98/ 25314	International filing date (day/month/year) 27/11/1998	(Earliest) Priority Date (day/month/year) 28/11/1997
Applicant WISCONSIN ALUMNI RESEARCH FOUNDATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

CDNAS AND PROTEINS BELONGING TO THE BHLH-PAS SUPERFAMILY OF TRANSCRIPTION REGULATORS AND METHODS OF USE

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1
☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/25314

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see additional sheet, invention 1.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 9-12,27-29 completely, and 1-8,17-23, 30-39 partially

MOP proteins 2-5 and nucleic acid encoding them, expression vectors comprising said nucleic acids, cells transformed with said vectors, oligonucleotides of 10-100 nt which hybridize to said nucleic acids, and antibody against said proteins.

2. Claims: 13 completely, and 1-8,17-23 partially

MOP-6 protein and nucleic acid encoding it, expression vector comprising said nucleic acid, cell transformed with said vector, oligonucleotide of 10-100 nt which hybridizes to said nucleic acid, antibody against said protein.

3. Claims: 14,24-26 completely, and 1-8,17-23 partially

MOP-7 protein and nucleic acid encoding it, expression vector comprising said nucleic acid, cell transformed with said vector, oligonucleotide of 10-100 nt which hybridizes to said nucleic acid, antibody against said protein.

4. Claims: 15 completely, and 1-8,17-23,30-34 partially

MOP-8 protein and nucleic acid encoding it, expression vector comprising said nucleic acid, cell transformed with said vector, oligonucleotide of 10-100 nt which hybridizes to said nucleic acid, antibody against said protein.

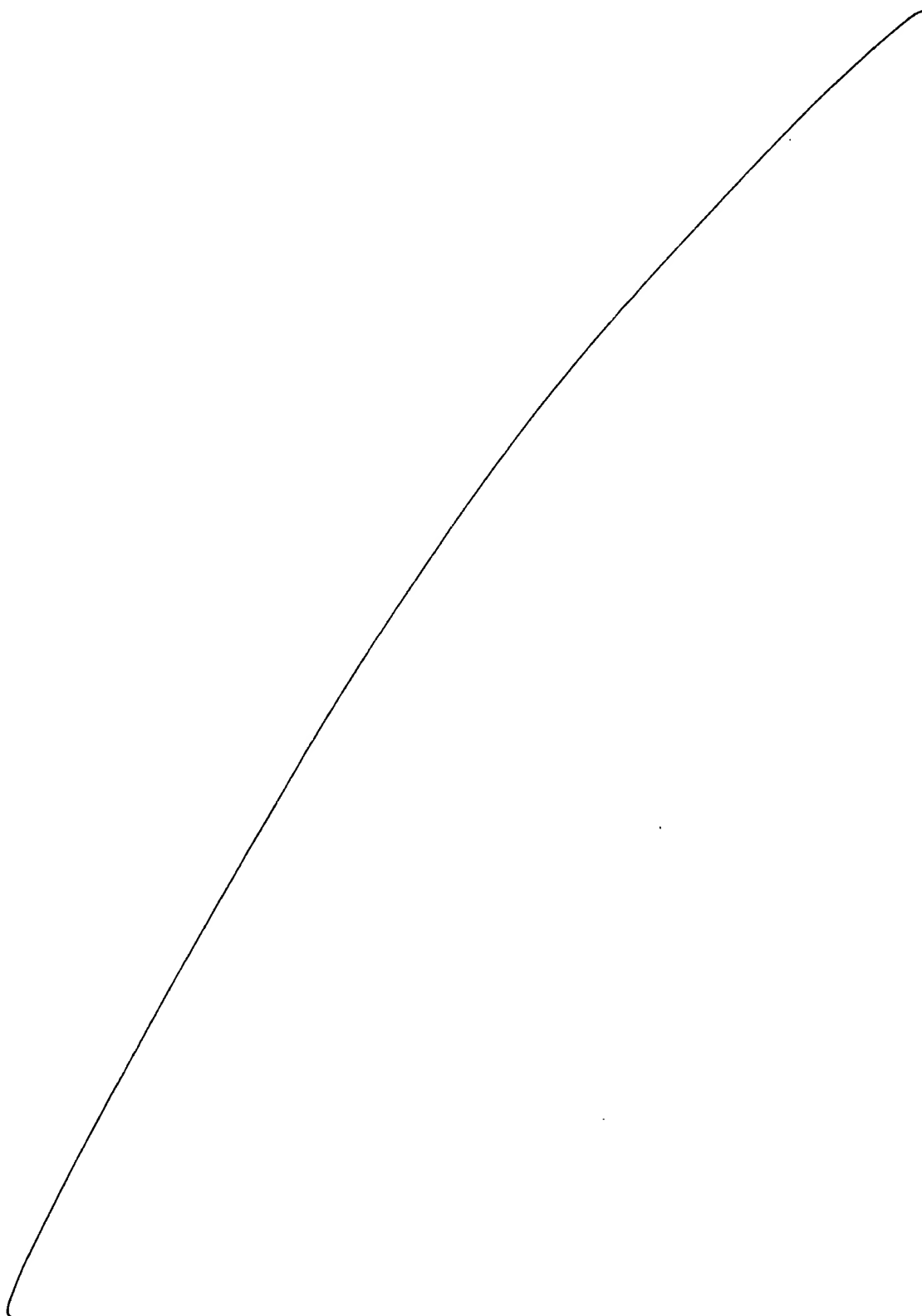
5. Claims: 16 completely, and 1-8,17-23,35-39 partially

MOP-9 protein and nucleic acid encoding it, expression vector comprising said nucleic acid, cell transformed with said vector, oligonucleotide of 10-100 nt which hybridizes to said nucleic acid, antibody against said protein.

6. Claims: 40-43

Methods for determining if a test compound regulates red blood cell synthesis, glucose metabolism, angiogenesis, or circadian function, comprising expression in a recombinant cell of the two binding partners of a pair of MOP proteins, whereby the host also comprises a reporter gene construct with a promoter which carries an E-box or hypoxia responsive transcription control element (HRE), exposure of the cell to said compound, and assessing expression levels of said reporter gene.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210



INTERNATIONAL SEARCH REPORT

International Application No.

US 98/25314

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/47 C12N15/11 C07K16/18 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOGENESCH, J.B. ET AL.: "Characterization of a subset of the basic-helix-loop-helix-PAS superfamily that interacts with components of the dioxin signaling pathway" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 13, 28 March 1997, pages 8581-93, XP002100642 see the whole document ---	1-12, 17-21, 27-40, 42,43
X	TIAN, H. ET AL.: "Endothelial PAS domain protein 1 (EPAS1), a transcription factor selectively expressed in endothelial cells." GENES AND DEVELOPMENT, vol. 11, no. 1, 1 January 1997, pages 72-82, XP002100643 see abstract; figures 1,5 ---	1-9,17, 18,20, 21,27-29
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

22 April 1999

Date of mailing of the international search report

01.10.1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Smalt, R

INTERNATIONAL SEARCH REPORT

International Application No

US 98/25314

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M EMA ET AL: "A novel bHLH-PAS factor with close sequence similarity to hypoxia-inducible factor 1-alpha regulates the VEGF expression and is potentially involved in lung and vascular development" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 94, April 1997, pages 4273-4278, XP002096344	1-9,17, 18,20,21
A	see page 4275, right-hand column, paragraph 3 - page 4276, right-hand column; figure 1A	42,43
X	IKEDA, M. ET AL.: "cDNA cloning and tissue-specific expression of a novel basic helix-loop-helix/PAS protein (MBAL1) and identification of alternatively spliced variants with alternative translation initiation site usage." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 233, no. 1, April 1997, pages 258-64, XP002100827 see figures 2,3	1-8,10, 17,18, 20,21, 35-39
X	ZHOU, Y-D ET AL.: "Molecular characterization of two mammalian bHLH-PAS domain proteins selectively expressed in the central nervous system" PROC.NATL.ACAD.SCI.USA, vol. 94, January 1997, pages 713-8, XP002100644 cited in the application see the whole document	1-8,11, 12,17, 18,20, 21,30-34
X	ANTONSSON, C. ET AL.: "Constitutive function of the basic helix-loop-helix/PAS factor ARNT" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 23, 9 June 1995, pages 13968-72, XP002100645 see page 13969, left-hand column, paragraph 2 - page 13971, right-hand column, paragraph 1; figures 3,4	22,23,40

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INTERNATIONAL SEARCH REPORT

International Application No

US 98/25314

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WANG, G.L. ET AL.: "Hypoxia-inducible factor 1 is a basic-leix-loop-helix-PAS heterodimer regulated by cellular O₂ tension"</p> <p>PROC.NATL.ACAD.SCI.USA, vol. 92, June 1995, pages 5510-4, XP002100646 cited in the application see abstract see page 5510, right-hand column, paragraph 1; figures 1,2 see page 5514, left-hand column, paragraph 2</p>	22,23
P,X	<p>--- US 5 695 963 A (MCKNIGHT STEVEN L ET AL) 9 December 1997 cited in the application see whole document, particularly claim 4</p>	1-9,17, 20,21, 27-29
P,X	<p>--- HOGENESCH, J.B. ET AL.: "The basic-helix-loop-helix-PAS orphan MOP3 forms transcriptionally active complexes with circadian and hypoxia factors."</p> <p>PROC.NATL.ACAD.SCI.USA, vol. 95, 1998, pages 5474-9, XP002100648 see the whole document</p>	1-8,10, 11,17, 18,20, 21,30-39
P,X	<p>--- WO 98 31804 A (UNIV TEXAS) 23 July 1998</p> <p>see page 17 - page 19; claims 1-9 -----</p>	1-8,11, 12,17, 18,20, 21,30-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

US 98/25314

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5695963	A	09-12-1997	AU 6242098 A WO 9831701 A	07-08-1998 23-07-1998
WO 9831804	A	23-07-1998	US 5840532 A AU 5926898 A	24-11-1998 07-08-1998